Remarks

Entry of the foregoing amendment and reconsideration of the subject application is respectfully requested. The present amendment cancels claims 2 and 34 and amends claims 1, 3, 33, 35 and 70. Claims 23, 30, 31, 53, 60 and 61 were previously canceled. Therefore, upon entry of the foregoing amendment, claims 1, 3-22, 24-29, 32, 33, 35-52, 54-59 and 62-71 remain pending in the subject application. Of these, claims 10, 11, 19, 38, 39 and 49 have been withdrawn from consideration as directed to non-elected subject matter. The Examiner is respectfully requested to note that the "Office Action Summary" (Form PTO-326) specifies, in item "4a)," that claims 20 and 23 have been withdrawn from consideration. Claim 20 has been examined and claim 23 was canceled by the amendment filed in response to the last Office Action. Therefore, neither claim 20 nor claim 23 has been withdrawn from consideration.

Rejection of claims 1, 4-7, 12-18, 20-22, 24-29, 32, 33, 40-48, 50-52, 55-59 and 62-69 under 35 U.S.C. §103(a) over WO 00/61141 to Au et al.

Claims 1, 4-7, 12-18, 20-22, 24-29, 32, 33, 40-48, 50-52, 55-59 and 62-69 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious in view of WO 00/61141 to Au *et al.* ("Au et al."). Reconsideration and withdrawal of this ground of rejection is respectfully requested.

Au et al. published on October 19, 2000. The subject application was filed April 10, 2001 and claims priority under 35 U.S.C. § 119(e) to provisional application ser. no. 60/195,920, filed April 10, 2000 ("the '920 provisional application"). Au et al. published later than the filing date of the '920 provisional application, and Au et al., therefore, is not a proper prior art reference against any claim in the subject application entitled to the filing date of the '920 provisional application. Applicants' amendments and remarks herein are, therefore, not to be construed as an acquiescence by Applicants that Au et al. is a proper prior art reference as to any claim in the subject application.

Even if Au et al. were a proper prior art reference, it is respectfully submitted that the

pending claims, upon entry of the foregoing amendment, are patentable over Au et al. alone or in combination.

Claims 1 and 33 are the only independent claims in the subject application. Claim 1 is directed to a composition for local administration of anti-tumor chemotherapeutic to a patient and claim 33 is directed to a corresponding method for local administration of anti-tumor chemotherapeutic to a patient. Each of claims 1 and 33 has been amended to recite that the suspending solution comprising the apoptosis-inducing chemotherapeutic agent is combined with an amount of a plasma protein effective in increasing the aqueous solubility of the apoptosis-inducing chemotherapeutic in the suspending solution. Claims 1 and 33 have thus, in effect, been amended to incorporate the features of claims 2 and 34 formerly dependent on claims 1 and 33, respectively. Claims 2 and 34 have, accordingly, been canceled.

It is respectfully submitted that the Au et al. neither teaches nor suggests a composition and/or a method for local administration of anti-tumor chemotherapeutic to a patient as recited in claims 1 and 33, respectively, as amended.

The Examiner correctly observes that Au et al. does not teach a formulation, as claimed in claims 1 and 33. Nonetheless, the Examiner maintains that Au et al. suggests such a formulation.

At page 4 of the Office Action, the Examiner states:

> First Au *et al.* teaches the importance of a formulation comprising both an apoptosis inducing agent and a chemotherapeutic agent (which can be the same drug). Second, Au *et al.* teaches that the apotosis [sic] agent must have time to cause apoptosis, followed by the release of the therapeutic agent. Third, Au *et al.* teach that the two components can be administered from the same dosage form, but it is important that the apoptosis inducing agent be released first. Therefore, this clearly calls for a dosage form with immediate release of the apoptosis inducing agent, followed by sustained release of the therapeutic agent. Relying on Au *et al.*'s teaching of suspension formulations and microparticles, one of ordinary skill in the art would clearly have the motivation to create sustained release microspheres comprising the therapeutic agent, to be suspended in a solution comprising the apoptosis inducing agent, so as to allow immediate release of the apoptosis inducing

> agent and sustained release of the therapeutic. Au *et al.* does not provide specific guidance for this formulation, but it is clearly suggested in the language of the specification. Therefore, this invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully disagree with the Examiner's conclusion of obviousness of in view of Au et al.

At col. 14, lines 8-13, Au et al. sates that a therapeutic agent and an apoptosis inducing agent can be "formulated together" and that "[i]n such an embodiment, the apoptosis agent is typically in a quick formulation and the therapeutic agent is typically in a slow release formulation...". Assuming, *arguendo*, that Au et al.'s reference to "formulated together" is interpreted to suggest that both an apoptosis inducing agent and a therapeutic agent can be formulated in the same dosage form, it is respectfully submitted that Au et al. provides no guidance to achieve this end. At best, Au et al. merely provides a broad suggestion of a single dosage form providing immediate release of the apoptosis inducing agent and sustained or delayed release of the therapeutic agent (which may be the same). Au et al. certainly does not teach or suggest a composition, as recited in claims 1 and 33, in which microspheres incorporating the at least one anti-tumor chemotherapeutic are suspended in a solution comprising the at least one apoptosis-inducing chemotherapeutic and a plasma protein effective to increase the aqueous solubility of the apoptosis-inducing chemotherapeutic agent.

Merely because Au et al. discloses, at page 24, that the apoptosis inducing agent and/or the therapeutic agent may be in the form of nanoparticles or larger microparticles, and one of ordinary skill in the art might deliver such nanoparticles or microparticles as a suspension in, e.g., a liquid carrier, does not provide any suggestion of also incorporating in the suspending solution an apoptosis-inducing agent and an amount of a plasma protein effective to increase the aqueous solubility of the apoptosis-inducing chemotherapeutic agent.

While Au et al. discloses that the apoptosis-inducing agent, when administered simultaneously with the therapeutic agent, is preferably in a quick release formulation, the only

quick release formulations specifically identified in Au et al. are the micro- and nanoparticle formulations. *See* Au et al., page 13, line 27-page 14, line 2. Thus, rather than suggesting incorporation of the apoptosis-inducing agent in the solution suspending the microspheres as recited in claims 1 and 33, Au et al. suggests incorporating the apoptosis-inducing agent in the form of nano- or microparticles.

Because Au et al. does not reasonably teach or suggest a composition, as recited in claims 1 and 33, in which microspheres incorporating the at least one anti-tumor chemotherapeutic are suspended in a solution comprising the at least one apoptosis-inducing chemotherapeutic and a plasma protein effective to increase the aqueous solubility of the apoptosis-inducing chemotherapeutic agent, it is respectfully submitted that the obviousness rejection over Au et al. is improper and should be withdrawn. It is respectfully submitted that claims 4-7, 12-18, 20-22, 24-29 and 32, at least by virtue of their dependency from independent claim 1, and claims 40-48, 50-52, 55-59 and 62-69, at least by virtue of their dependency from independent claim 33, are also patentable over Au et al.

Rejection of claims 8, 9, 36 and 37 under 35 U.S.C. §103(a) over WO 00/61141 to Au et al. in view of U.S. Patent No. 6,277,391 to Seo et al.

Claims 8, 9, 36 and 37 have been rejected as allegedly being obvious over Au et al. in view of U.S. Patent No. 6,277,391 to Seo et al. Reconsideration and withdrawal of this ground of rejection is respectfully requested.

Claims 8 and 9 depend from independent claim 1 and claims 36 and 37 depend (either directly or indirectly) from independent claim 33. It is respectfully submitted that Seo et al. does not alleviate the deficiencies of Au et al., as discussed above. In particular, it is respectfully submitted that the combination of Au et al. in view of Hegedus et al. does not teach or suggest a composition, as recited in claims 1 and 33, in which microspheres incorporating the at least one anti-tumor chemotherapeutic are suspended in a solution comprising the at least one apoptosis-inducing chemotherapeutic and a plasma protein effective to increase the aqueous solubility of

the apoptosis-inducing chemotherapeutic agent.

Claims 8, 9, 36 and 37 are, therefore, patentable at least for the reasons set forth above in regard to claims 1 and 33.

Rejection of claims 2, 3, 34, 35, 70 and 71 under 35 U.S.C. §103(a) over WO 00/61141 to Au et al. in view of WO 99/13914 to Hegedus et al.

Claims 2, 3, 34, 35, 70 and 71 have been rejected as allegedly being obvious over Au et al. in view of WO 99/13914 to Hegedus et al. Reconsideration and withdrawal of this ground of rejection is respectfully requested.

This rejection is moot with respect to claims 2 and 34, which have been canceled by this response. Claims 3 and 71 depend from independent claim 1 and claims 35 and 70 depend from independent claim 33. It is respectfully submitted that Hegedus et al. does not alleviate the deficiencies of Au et al., as discussed above. In particular, it is respectfully submitted that the combination of Au et al. in view of Hegedus et al. does not teach or suggest a composition, as recited in claims 1 and 33, in which microspheres incorporating the at least one anti-tumor chemotherapeutic are suspended in a solution comprising the at least one apoptosis-inducing chemotherapeutic and a plasma protein effective to increase the aqueous solubility of the apoptosis-inducing chemotherapeutic agent.

Claims 3, 35, 70 and 71 are, therefore, patentable at least for the reasons set forth above in regard to claims 1 and 33.

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CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that this application is now in condition for allowance, which action is earnestly solicited. The Examiner is invited to contact the undersigned attorney to discuss any matter concerning this application.

The Commissioner is hereby authorized to charge any fees which may be necessary for consideration of this paper or to credit any overpayment to Kenyon Deposit Account No. 11-0600.

Respectfully submitted,

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